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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/196,154 11/16/95 LIVINGSTON

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HM22/1006

EXAMINER

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ART UNIT	PAPER NUMBER
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1645

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DATE MAILED:

10/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No.	Applicant(s)
	08/196,154	Livingston et al
	Examiner DUFY	Group Art Unit 1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- Responsive to communication(s) filed on 7-26-99.
- This action is FINAL.
- Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- Claim(s) 69 - 94 is/are pending in the application.
- Of the above claim(s) _____ is/are withdrawn from consideration.
- Claim(s) _____ is/are allowed.
- Claim(s) 69 - 94 is/are rejected.
- Claim(s) _____ is/are objected to.
- Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- The proposed drawing correction, filed on _____ is approved disapproved.
- The drawing(s) filed on _____ is/are objected to by the Examiner.
- The specification is objected to by the Examiner.
- The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - All Some* None of the CERTIFIED copies of the priority documents have been received.
 - received in Application No. (Series Code/Serial Number) _____.
 - received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Attachment(s)

- Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ Interview Summary, PTO-413
- Notice of Reference(s) Cited, PTO-892 Notice of Informal Patent Application, PTO-152
- Notice of Draftsperson's Patent Drawing Review, PTO-948 Other _____

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Office Action Summary

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Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 7-26-99 has been entered.
2. The amendment filed 7-26-99 has been entered into the record. Claims 69-96 are pending and under examination.

Objections or Rejections Maintained

Specification

3. The prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/19/98 (see Paper No. 16).

Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. Until applicants submit a proper Figure said objection is maintained.

Double Patenting

4. Claims 69-96 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the all the claims of copending Application No. 08/477,097.

Applicants assert that the added new claims in the copending application obviate the obvious type double patenting since the claims in the 097' application are directed to a

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conjugation partner that is an immunogenic protein-based carrier. Applicants' arguments are not persuasive since BSA and KLH have long been used as immunogenic protein based carriers for the conjugation of substances to allow for the generation of specific immune responses. These carriers have long been discussed in general textbooks such as Antibodies: A Laboratory Manual by Harlow and Lane (1988, Cold Spring Harbor Laboratories, page 129). The claims of the instant application encompass conjugating the ceramide portion of GM2 via a variety of linkages as recited the claims in copending application 08/477,097 and the substitution of KLH for the a generic immunogenic protein-based carrier of the 097' application is an obvious variation.

Applicants amendments are insufficient to remove the rejection.

5. Claims 69-96 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims all the claims of copending Application Nos. 08/475,784.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the prior Office Actions. Applicants argue that the '784 applications are directed to compositions which are gangliosides and not GM2 or GD2. It is respectfully submitted that the ganglioside of the '784 application is selected from the group consisting of GM2.... etc, as is admitted by applicants in the traversal of the double patenting rejection. Thus, the applications have clearly overlapping subject matter in these two applications.

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6. Claims 69-96 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over all the claims of copending Application Nos. 08/481,809 in view of Livingston et al. (Cancer Research, 149:7045-7050, 1989

Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth below. The '809 application claims compositions and methods using gangliosides in general linked via the ceramide portion of the ganglioside to KLH and to an adjuvant, a carbohydrate saponin and a pharmaceutically acceptable carrier. The instantly claimed compositions drawn to specific species of gangliosides (GM2 and GD2) conjugated to KLH anticipate admixed with a carbohydrate saponin and a pharmaceutically acceptable carrier. It would have been *prima facie* obvious to attach either of the gangliosides GM2 or GD2 through a ceramide carbon because Livingston et al teach that these are medically important gangliosides and immune responses generated against them are able to treat cancer and GM2 and GD2 are species of gangliosides.

7. The rejection of claims 69-71 and 72-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed 6/13/96 (see Paper No. 8).

Applicants arguments' have been carefully considered. Applicants' again argue make and test. This is again not persuasive for reasons already extensively made of record in the previous response and reiterated below.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth

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factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). Rudinger et al. Teaches "particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstakingly experimental study" (see page 6). Salgaller et al teach modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. Fox et al. Teach methods for determining fragments which have antigenic activity is unpredictable. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives and fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

Contrary to applicants arguments it is reasonable to conclude an undue burden is required to screen for positions within the sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited and the result of such modifications is unpredictable as exemplified by the teachings of Lazar et al., Burgess et al., Rudinger et al., and Salgaller et al. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein.

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The specification does not support the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does not disclose the following :

- the general tolerance to modification and extent of such tolerance;
- specific positions which can be predictably modified; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims broadly including any number of deletions, additions, and/or substitutions of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

Applicants cite to page 12, lines 4-13 of the specification for support of using derivatives of KLH. Said disclosure is not commensurate in scope with the claimed invention. Said cite makes reference only to linking KLH to an "immunological adjuvant" **and not** amino acid modifications (i.e deletions, substitutions) of KLH. As set forth above the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). For the reason set forth above and in the last Office Action said rejection is maintained.

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As to claims 81-86, the claims are enabled for the use of the composition only for the treatment of cancer but are NOT enabled for the prevention of cancer, for reasons made of record in Paper No. 8, mailed 6-13-96.

8. Claims 69-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants point to page 32, lines 13-18 and page 12, lines 22-26 for support for the now claimed invention. This is not persuasive, the passage at page 32, lines 13-18 provide for a *specific coupling procedure at the C-4 carbon of the sphingosine moiety of the ceramide to the ε-aminolysyl group of a protein* (ozonolysis, production of a functional aldehyde group and coupling to an ε-aminolysyl group on a protein by reductive amination. The passage at page 12, lines 22-26 in combination with the passage at page 32, lines 13-18 does not support a broad coupling to any generic portion of the ceramide backbone of the ganglioside, by any generic means by cleavage of any double bond (i.e. C=O) and coupling by any linkage process. The written description at page 12 and 32 does not support by way of written description, convey that applicants had at the time of filing contemplated any means of coupling to any portion of the ceramide, a concept that is now broadly claimed. Applicants were clearly not in possession of that which is now broadly claimed. Correction is required.

Claim Rejections - 35 USC § 103

9. The rejection of claims 69-81 and 83-96 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars

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in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

Livingston et al (Cancer Research) teach a composition administered to melanoma patients for stimulation the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (page 7046-7048). Livingston et al teach that the composition for treatment is administered at a concentrations of 100, 200, or 300 ug with an adjuvant, Bacillus-Calmette-Geurin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, (p 7046, column 1, paragraph 3, and paragraph bridging p 7046-47). Livingston et al teach that melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (pate 7047, paragraph bridging columns 1-2). Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2). Livingston et al differ by not teaching the conjugation of the GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on Keyhole Limpet Hemocyanin (KLH) in a composition and using this composition for treatment.

Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). Ritter et al teaches discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-

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dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose or the amino group bearing glass beads.

Ritter et al (1990) teach that GD3 lactone is more immunogenic than GD3.

Livingston et al (U.S. Patent No. 5, 102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28).

Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose or the amino group bearing glass beads.

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

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Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptic reactivity of the ganglioside derivative with antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Livingston et al by conjugating the GM-2 to KLH by covalently coupling GM2 to KLH by substituting GM2 for the globoside and KLH for the aminoethyl agarose to produce a GM-2-KLH conjugate by means of the olefinic bond of the sphingosine moiety of the GM2 (i.e. the instant ceramide double bond) and the ε-aminolysyl groups present in the KLH protein using the method of Liane et al and add QS-21 as an adjuvant to the GM-2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages by Ritter et al (1991) and adding the QS-21 would be advantageous because it provides for a higher antibody response than the commonly used adjuvant use by Kensil et al and QS-21 provides the advantages that it is not toxic to animals as is taught by Marciani et al. It also would have been *prima facie* obvious to use doses of between 10 and 80 ug of QS-21 in the composition and optimize the dose accordingly because the immune response with QS-21 plateaus at doses between 10-80 ug and optimization of the weight ratio of the components of the composition to provide an optimal response is well within the ordinary skill in the art and use the composition as modified supra for treatment of melanoma as taught by Livingston et al (Cancer Research). It also would have been *prima facie* obvious to one of ordinary skill in the art to substitute any one of GM3, GD2, GD3, or O-acetyl GD3 for the GM2 ganglioside in the composition and method as combined supra because they are all prominent cell-membrane components of melanomas as taught by Livingston et al (U.S. Patent No.

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5,102,663) and one of ordinary skill in the art would react with the melanoma cells. It would have also been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GD3 lactone for the GM2 ganglioside in the composition because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990) and would be expected to product an enhanced antibody response as compared to GD3. Optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is will within the skill of the ordinary artisan. One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance immunogenicity is routine in the art and Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptic reactivity with antibodies.

10. The rejection of claim 82 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem, 79(6):1253-1261, 1976) as applied to claims 69-81 and 83-96 above and further in view of Irie et al. (U.S. Patent No 4,557,931).

The teachings of Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem, 79(6):1253-1261, 1976) are set forth supra. The combination differs by not teaching the administration of the composition for treating cancer of epithelial origin or for producing antibodies to gangliosides found in the stroma of cancer.

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Irie et al teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the GM-2-KLH conjugate/ QS-21 composition or other ganglioside conjugate/QS-21 composition as combined *supra* to patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e. breast carcinomas) because the ganglioside GM-2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

Status of Claims

11. All claims stand rejected.

12. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
October 6, 1999

Patricia A. Duffy
Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600